REMARKS/ARGUMENTS

This is in response to the Office Action mailed January 5, 2007. Claims 1-10 are pending in the application, and are listed above. No claims are amended, added or deleted. Thus, original claims 1-10 remain pending and active.

Claim Rejections - 35 USC § 103

Claims 1-10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gidwani et al. US 6,828,334 (Gidwani).

According to the Examiner, Gidwani teaches a pharmaceutical composition containing fenofibrate in the form of an inclusion complex with methylated beta cyclodextrin (Example 6). The Examiner further states that the inclusion complex can be administered as pharmaceutical formulations in the form of tablets or in the form of granules inside a capsule (column 5, lines 20-45). Gidwani is said to differ from the instantly claimed invention in that (1) Gidwani is silent on the use of a crystalline cyclodextrin and (2) Gidwani does not teach liquid formulations.

The Examiner is of the opinion that the present claims merely recite a function or property (*i.e.*, physical form) that is inherently possessed by things in the prior art and, therefore, claims drawn to those things do not distinguish over prior art. The Examiner asks applicants to prove that subject matter shown to be in prior art **does not** possess the recited characteristics relied for patentability. That is, applicants have the burden of persuasion to compare materials in order to establish unexpected properties of crystalline forms of methylated beta-cyclodextrin. The Examiner further opines that the formulation of the composition of Gidwani into a cream or liquid is well within the purview of one of ordinary skill in the art.

In response, Applicant respectfully traverses this rejection and provides the requested evidence that the prior art does not inherently teach the claimed invention nor suggest it. In Example 6, Gidwandi teaches a randomly-methylated beta cyclodextrin. Gidwandi states: "The procedure of Example 1 was followed using

randomly methylated beta cyclodextrin (590 gm) Cerestar Inc., USA) to obtain an inclusion complex..."(Column 7, lines 10-11, emphasis added)

Applicant asserts that randomly-methylated beta-cyclodextrin is an amorphous product, which is not the same thing as a crystalline product. To support this assertion, applicant attaches an excerpt from *Cyclodextrins in Pharmacy*, Froemming and Szejtli, Springer (publisher) (1994) (Appendix A), which explains in chapter 2.2 that beta – cyclodextrin has to be modified to improve solubility and prevent its crystallization. It states that "[t]he random substitution...produces a very heterogenous, noncrystallizable product..." It further discusses randomly methylated beta-cyclodextrins (referred to as RAMEB) and notes that recently, **amorphous, noncrystallizable RAMEB** was made that is available at an acceptable price. In view of these discussions about the non-crystallizable nature of randomly methylated beta-cyclodextrins, it is clear that what Gidwani teaches is an amorphous product.

Aside from this point of clarification about what Gidwandi actually discloses, the above excerpts are relevant for teaching against the use of crystallized cyclotextrins. Arguably, one reading this 1994 text book on the pharmaceutical use of cyclodextrins would have been motivated to pursue the use of amorphous, rather than crystalline cyclodextrins. As such, these teachings support a finding of non-obviousness with regard to the present claims.

Additionally, because Gidwandi teaches an amorphous product, such product is the same as what applicant describes, for comparative purposes, in the present specification. That is, Gidwandi teaches a product that is comparable to Cavasol W7M, which is a randomly methylated and amorphous product. (Attached in Appendix B is the product sheet for Cavasol, which states that it is a "statistically methylated cyclodextrin" i.e. randomly methylated. The present specification shows that applicant's invention out-performs amorphous Cavasol W7M. For instance, Table 1 shows the solubilization potency of the crystalline methylated beta-cyclodextrin with carbamazepine compared to three commercially available cyclodextrins, including Cavasol W7M. When compared on a weight basis, the crystalline methylated beta-

cyclodextrin is clearly better than the other products. Arguably, one would not have expected such superior results, which therefore further support the non-obviousness of the present invention.

CONCLUSION

In light of the above comments, supporting documentation and the data in the specification, applicant respectfully requests the Examiner to reconsider and withdraw the rejection for obviousness and that a timely Notice of Allowance should be issued in this application. Should the Examiner have any questions, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date: March 23, 2007

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 08-1641 for any such fees; and applicants hereby petition for any needed extension of time.

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APPENDIX A

2.2. Effects of Chemical Modification on the Properties of CDs

βCD itself shows an anomalously low solubility in water. While, at room temperature in 100 ml water, about 14 g αCD, or 23 g γCD can be dissolved, only 1.8 g of βD dissolves. The βCD torus is the most rigid CD structure, therefore it is more inclined to crystallization than the other two CDs. All —C_2OH groups form hydrogen bonds with —C_3OH groups of the neighbouring glucopyranose units. The βCD forms head-to-head dimers even in aqueous solution. The solubility of many poorly soluble drugs shows a several fold increase when complexed with βCD, but this means not more than about 0.1–0.2 g/100 ml dissolved complex. This is one of the reasons why injectable solutions cannot be prepared using βCD. The other reason is that parenterally administered βCD is not metabolised, but accumulates in the kidneys as insoluble crystalline cholesterol complexes, resulting in severe nephrotoxic symptoms.

All this means that the βCD has to be modified: both to improve its solubility and to prevent its crystallization. Fortunately, almost any chemical or enzymatic modification of the βCD, substitution of any hydroxyl group(s) by any – even expressly hydrophobic – alkyl or aryl ether or ester group results in a dramatic increase in solubility. The random substitution, which technically is more feasible than the preparation of any well-defined homogeneous derivative, produces a very heterogeneous, noncrystallizable product, which cannot form kidney-damaging crystalline cholesterol complexes. Therefore the feasible way to use βCD in parenteral formulations is its derivatization. Hundreds of derivatives have been prepared, but for technical purposes only the nontoxic, nonhaemolytic, relatively simple derivatives can be taken into account.

The first highly soluble CD derivative dedicated to pharmaceutical uses was the heptakis (2,6-di-*O*-methyl)-βCD = DIMEB (Figure 2-1). For many highly hydrophobic drugs this solubilizer turned out to be most effective (Table 2-I), remaining unexcelled even today; but regrettably this CD derivative shows a high surface activity and a high affinity for cholesterol; even at 1 mg/ml concentration this results in haemolysis of the human erythrocytes. A further problem is that its preparation is complicated and expensive. In most cases, however, it can be substituted effectively by the heterogeneous, randomly methylated βCD (RAMEB), which is already produced industrially.

A second group of βCD derivatives intended for parenteral administration is represented by the dihydroxypropyl derivatives, prepared by the reaction of epichlorohydrin with CDs in alkaline aqueous solution (Figure 2-1). These derivatives – particularly those dihydroxypropyl derivatives which also contain some ionic group (like carboxymethyl or diethylaminoethyl groups) – are excellent solubilizers for

The less hygroscopic nature of the methylated cyclodextrins in comparison to the natural CD is an advantage, since it is moisture sorption that initiates the hydrolytic decomposition of drugs in the solid state.

While, in many cases, hydrolytic reactions in aqueous solutions are accelerated by CDs, the methylated CDs in which the hydroxyl groups are blocked may cause an inhibition of the reaction rather than an acceleration (see Section 4.3.5).

In contrast to the underivatized CDs, both DIMEB and TRIMEB have surfactant activity.

The interactions between drugs and TRIMEB have been studied less extensively.

Oral administration of DIMEB to rats and rabbits fed with large amounts of fats or vegetable oils, strongly improved the digestion and absorption of the fats. In bile duct ligated animals nearly normal fat digestion was also observed. DIMEB can possibly substitute for natural bile.

Recently the industrial production of the amorphous, noncrystallizable RAMEB (with a *DS* of 1.8–2.0) made this substance available at an acceptable price. Detailed toxilogical studies are in progress (in 1992). The parenteral administration of RAMEB will certainly remain restricted to nonhaemolytic concentrations, but its use in oral and external formulations is expected in the future. It certainly will be used widely in diagnostic preparations, in biotechnology, in cosmetics, etc.

2.4. Hydroxypropyl CDs

On reacting βCD in alkaline solution with propylene oxide a 2-hydroxypropyl group will be connected to one or more hydroxyls of the βCD, or to the hydroxyls of the 2-hydroxypropyl groups already linked to the βCD molecule. The degree of substitution characterizes such a heterogeneous product, and this can be expressed in different ways.

The substitution degree (*S*) expresses the number of substituted hydroxyls of one gluconyranose unit: it can be 1, 2 or 3.

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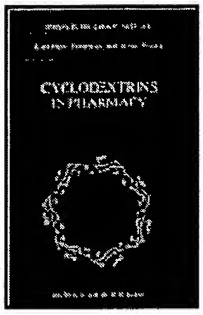
Cyclodextrins in Pharmacy By Karl-Heinz Frömming, József Szejtli

Summary



Preview this book

By Karl-Heinz Frömming, József Szejtli

Published 1994
Springer

Medical / Nursing

ISBN 0792321391

Nearly three thousand papers and patents are dedicated to the actual or potential uses of cyclodext pharmaceutical formulations. This is the first book written for pharmacists and pharmaceutical techr critically summarizes the enormous amount of literature available, but which can be used as a hand solutions to practical problems. The fundamentals -- chemistry of cyclodextrins and their derivatives chemical properties are condensed to the most relevant items in Chapters 1 and 2. Chapter 3 deals metabolism and toxicological properties of cyclodextrins. Chapter 4 explains the formulation, struct advantageous effects of the cyclodextrin inclusion complexes. Chapter 5 describes the methods for characterization of drug/cyclodextrin complexes. Chapters 6 and 7 are dedicated to the pharmacoki biopharmaceutical and technological aspects of drug/CD complexes. Chapter 8 treats the applicatic cyclodextrins in various drug formulations. The Appendix comprises a collection of recipes for any t This book is aimed at those who use cyclodextrins in drug formulations, to improve the properties o formulations, or who want to prepare quite new formulations.

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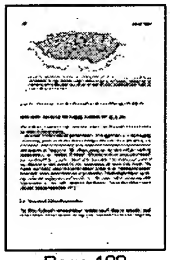

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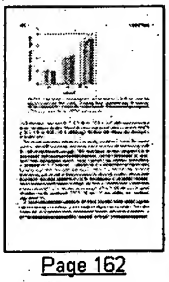

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APPENDIX B

WACKER FINE CHEMICALS

CAVASOL®

CAVASOL® W7 M Pharma

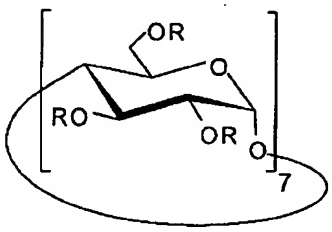
Characteristics

CAVASOL® W7 M Pharma is a statistically methylated ß-cyclodextrin derivative from Wacker-Chemie GmbH

Special characteristics

- Chemical name: methyl-ß-cyclodextrin cyclomaltoheptaose, methyl ether
- CAS-No.: 128446-36-6
- Appearance: white powder
- Average mol. wt: ~ 1310 (calc.)
- Solubility in water: > 200 g in 100 ml at 25°C
- Good solubility in: methanol, ethanol,acetone, pyridine, dimethyl sulfoxide, dimethyl formamide
- Bulk density ~ 0.2 – 0.3 g/ml
- Melting range: 160 – 190 °C (decomp)

Chemical structure



R = CH_3 or H

Product data

Parameter	Value
Clarity and color of an 10% aqueous solution	Clear and colorless (according to Pharm. Eur.)
Degree of substitution (per anhydro glucose unit):	1.7 – 1.9
Optical density of a 10% solution:	0.1 max. (350-600 nm); 1.0 max. (220-350 nm)
Acidity/alcalinity (40 ml of a 10% aqueous sol.)	No more than 0.5 ml of 0.1N NaOH No more than 0.5 ml of 0.1N HCl
Specific rotation in water[α]$_{D,20}$, 5% sol.	+ 164 +/- 3°
Reducing compounds(determined as dextrose):	0.5 % max.
β-Cyclodextrin:	0.1% max
Residual solvents	Methanol < 0.005%, methyl chloride < 1 ppm
Chloride content:	500 ppm max.
Heavy metals:	10 ppm max.
Loss on drying:	5.0 % max.
Residue on ignition (sulphated ash):	0.1% max.
Microorganisms:	100 /g max.
E. coli, P. aeruginosa, S. aureus	0 in 1 g
Salmonella sp.	0 in 10 g

WACKER FINE CHEMICALS

CAVASOL®

Storage

Storage at room temperature in sealed containers under dry conditions is recommended. CAVASOL® W7 M Pharma has a shelf life of twelve months from the date on the delivery note.
Continued storage beyond the designated shelf life does not necessarily mean the material cannot be used. However, it is imperative for reasons of quality assurance that the user checks product data of significance for the intended application.

Package

Units of 10kg

Additional information

Registration

ELINCS, TSCA, DSL/NDSL, MITI, AICS
DMF Type IV No. 15489

Tariff Numbers:

EU:	2940 00 00
India:	2940.00.00
South Korea:	2940.00.20.90
USA:	2940.00.60.00
Japan:	2940.00.010

Safety information

Detailed safety information is contained in each material data safety sheet, which can be obtained from our sales offices.

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The management system has been certified according to DIN EN ISO 9001 and DIN EN ISO 14001

Version 3.00 from 04-10-05 replaces Version 2.00 from 17-03-03

For technical, quality, or product safety questions, please contact:

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